National Cancer Institute

CLINICAL PROTEOMIC
TUMOR ANALYSIS CONSORTIUM

CPTAC Pre-Application Session

RFA-CA-15-021 (Proteome Characterization Centers)

RFA-CA-15-023 (Proteogenomic Data Analysis Centers)

***RFA-CA-15-022** (Proteogenomic Translational Research Centers)*

Time/Date: 12:00 p.m. - 3:00 p.m. (ET), Dec 11, 2015

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

http://proteomics.cancer.gov

Agenda

12:00 p.m. - 12:15 p.m.

Welcome and Introductions

Henry Rodriguez, Ph.D., M.B.A.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Opening Remarks

Douglas R. Lowy, M.D.

Acting Director, NCI, NIH

Agenda

12:15 p.m. - 3:00 p.m.

Progress and Opportunities in Cancer Proteomics

Henry Rodriguez, Ph.D., M.B.A.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Description of RFA-CA-15-021 (Proteome Characterization Centers)

Emily Boja, Ph.D.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Description of RFA-CA-15-023 (Proteogenomic Data Analysis Centers)

Chris Kinsinger, Ph.D.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Intellectual Property

Tom Stackhouse, Ph.D. and Charles Salahuddin, Ph.D., *Technology Transfer Center*

Financial/Grants Management

Mutema Nyankale, M.B.A., *Office of Grants Administration*

NOTICE (NOT-CA-16-004)

(RFA-CA-15-022 Update)

New application receipt date: May 11, 2016, by 5:00 PM local time of applicant organization (no late applications will be accepted)

Letters of Support: At the time of application submission, applicants must provide **letter(s) of support** for access to clinical trial specimens to be used in the proposed research.

- Guidance listed in Supporting Documents: (http://proteomics.cancer.gov/aboutoccpr/fundingopportunities/current/Reissuance-of-Clinical-Proteomic-Tumor-Analysis-Consortium)

Letter of Intent: April 11, 2016 (30 days prior to application due date)

Pre-application webinar: Jan 13, 2016; 12:00 p.m. - 2:00 p.m.

NOTICE (NOT-CA-16-004)
(RFA-CA-15-022 Update)

Pre-application webinar: Jan 13, 2016; 12:00 p.m. - 2:00 p.m.

Description of RFA-CA-15-022 (Proteogenomic Translational Research Centers)

Mehdi Mesri, Ph.D.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Additional representation

Investigational Drug Branch, Cancer Therapy Evaluation Program

- S. Percy Ivy, M.D., *Phase I Early Therapeutics Clinical Trials Network (ETCTN)*
- Jeff Moscow, M.D., *Phase II Early Therapeutics Clinical Trials Network (ETCTN)*
- James Zwiebel, M.D., *Chief*

Clinical Investigations Branch, Cancer Therapy Evaluation Program

- Elise Kohn, M.D., *National Clinical Trials Network (NCTN)*
- Meg Mooney, M.D., M.B.A., *Chief*

Diagnostic Biomarkers and Technology Branch, Cancer Diagnosis Program

- James Tricoli, Ph.D., *Chief*

Key Dates
(RFA-CA-15-021 & RFA-CA-15-023)

Application receipt date: *No late applications will be accepted.*

- RFA-CA-15-021 & RFA-CA-15-023 (Jan 27, 2016, by 5:00 PM local time of applicant organization)

Letter of Intent: 30 days prior to application due date

- RFA-CA-15-021 & RFA-CA-15-023 (Dec 28, 2015)

Reissuance Presentation to NCI Board of Scientific Advisors (BSA): June 24, 2015

- URL: http://videocast.nih.gov/summary.asp?Live=16424&bhcp=1
  - or Web Search Engine: “NIH VideoCasting and Podcasting;” In search field, enter “CPTAC”
- Time stamp: 4h:06min:21sec (40 min session)

Submitting Questions and Updates

Email questions after the presentation to cancer.proteomics@mail.nih.gov

Archived viewing of slides will be available through the website http://proteomics.cancer.gov

Sign up for updates at http://proteomics.cancer.gov/global/emailsignup

http://proteomics.cancer.gov

FOA Teaming & FAQ Site

Teaming Site

- Web-based system to facilitate initial communications and exploration of collaborative possibilities
  - Go to: http://proteomics.cancer.gov
  - Click on "**FOA Teaming Site**"
  - Participants submit basic set of information:
    - Position
    - Organization
    - General areas of expertise
    - Comments

Frequently Asked Questions (FAQs)

http://proteomics.cancer.gov

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Progress and Opportunities in Cancer Proteomics

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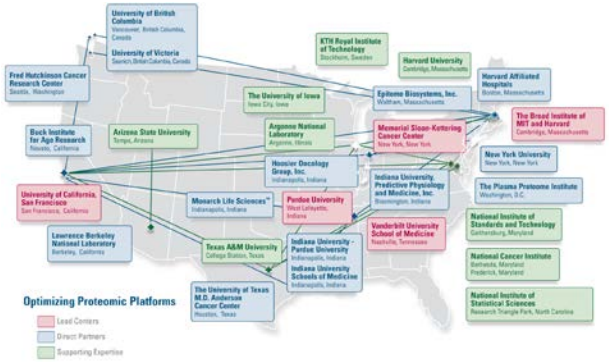
CPTAC program current scope

- NCI Signature Omics Programs (2006)
  - *Genomics:* **TCGA** - understand molecular basis of cancer through genomics. Pilot (3 cancer types) - ovarian, lung, and brain cancer
  - *Proteomics:* **CPTAC** - address lack of analytical rigor & reproducibility and community resources (data and reagents)
- Achieved through…
  - Proteomic Technology Assessment Centers - consortium of labs that coordinate, benchmark, and standardize platforms

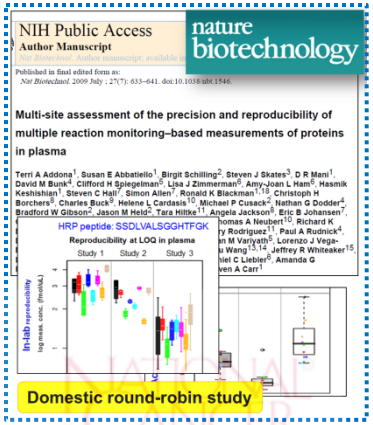


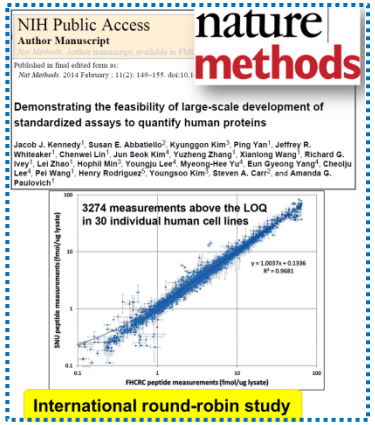
AACC FDA NIST

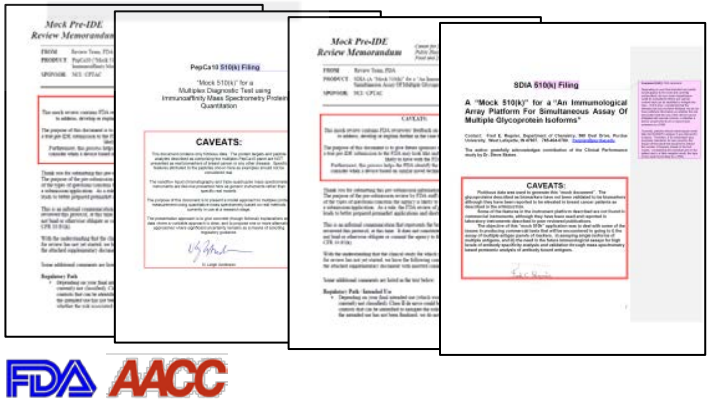
RIGOR & REPRODUCIBILITY

Selected research highlights

- Performance metrics of global mass spec (untargeted)[1-2]
- Precision, Reproducibility & Transferability of targeted mass spec (round-robin of MRM/SRM)[3-4]
- Open-source computational tool (Skyline) for designing targeted mass spec assays[5]
- Mock 510(k) device clearance documents in targeted proteomics[6]
- Data sharing policies (Amsterdam Principles)[7-8]







FDA AACC

References: [1] J Proteome Res. 2010; 9(2):761-776, [2] Mol. Cell Proteomics 2010; 9(2):255-241, [3] Nat Biotech 2009; 27(7):633-644, [4] Nat Methods 2014; 11(2):149-155, [5] Bioinformatics 2010; 26(7):966-968, [6] Clin Chem 2010; 56(2):165-171, [7] J Proteome Res. 2009; 8:3689-3692, [8] Mol. Cell Proteomics 2010; 10(12):O111.015446

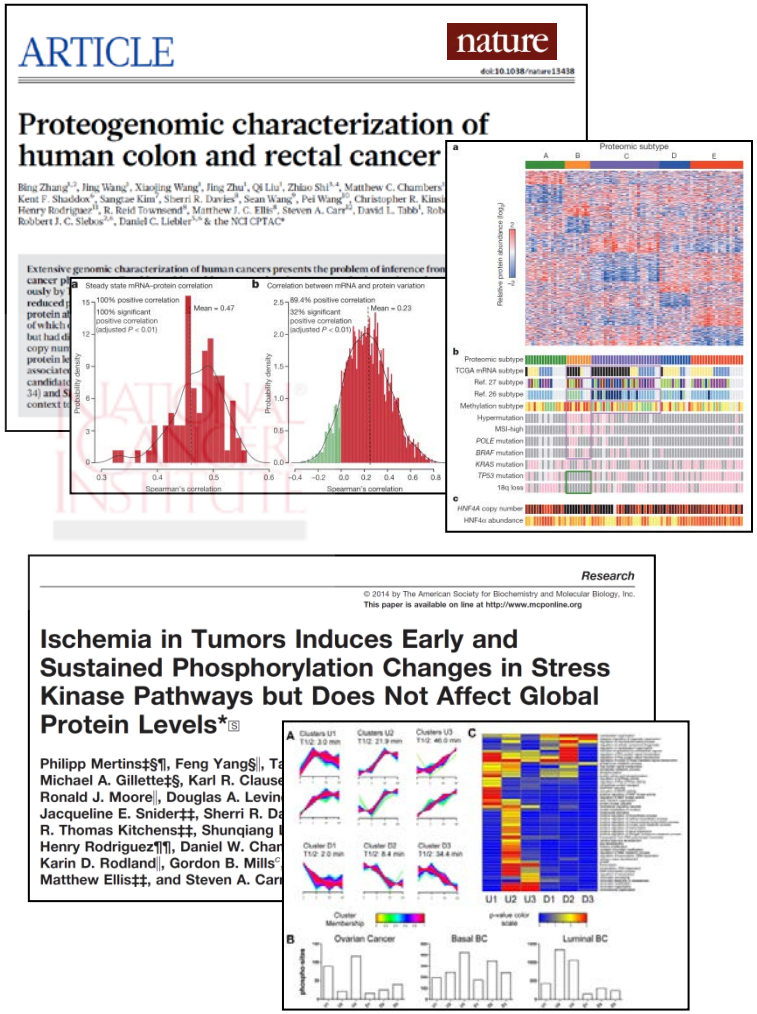
CPTAC program current scope

- CPTAC reissued (2011)
  - *Goal:* Elucidate proteogenomic complexity of tumors by identifying proteins that derive from alterations in cancer genomes [TCGA tumors: colorectal, ovarian and breast cancer]
  - *Underlying question:* Would additional biology be elucidated from deep proteomic analysis [CPTAC 1.0] on genomically characterized tumors [TCGA]?

- Achieved through…
  - Proteome Characterization Centers - labs coordinate standardized research activities
  - Samples (CRC - 95; OVC - 174; BRC - 105)
  - Community resources (data, assays, reagents)

Selected research highlights

- First comprehensive proteomic characterization of a tumor, with proteogenomic integration[1]
- Completed comprehensive proteomic characterization on two other cancer types (ovarian and breast), with proteogenomic integration (manuscripts under review)
- Understanding tumor pre-analytical variables[2]
- Data publicly available (all studies)



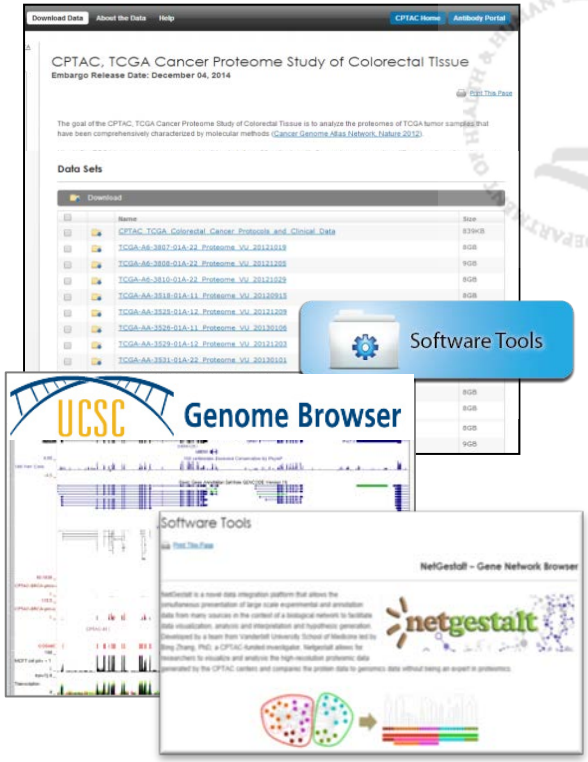
References: [1] Nature. 2014 Sep 18;513(7518):382-387; [2] Mol Cell Proteomics. 2014 Mar;13(3):907-917

Selected benchmark highlights
(generation/dissemination of community resources)

CPTAC Data Portal

6.2 TB raw files
(132 TB equivalent downloaded)

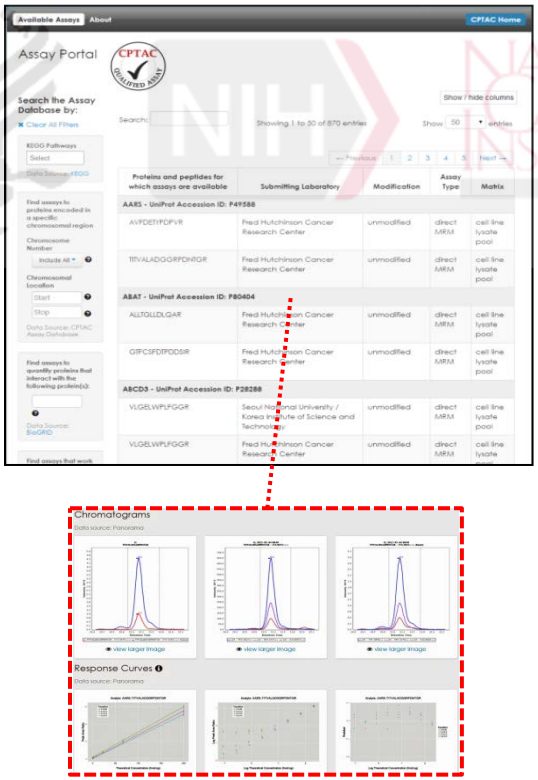
proteomics.cancer.gov



CPTAC Assay Portal

790 "fit-for-purpose" targeted assays
(4,800 users/month)

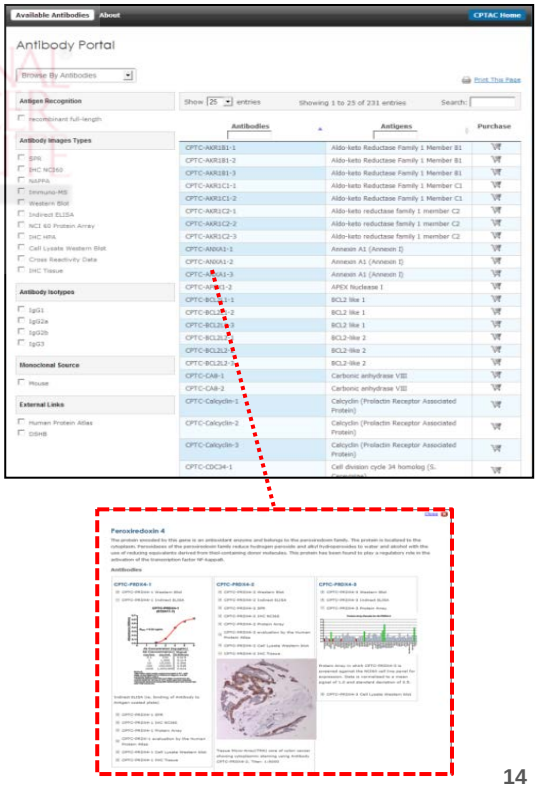
assays.cancer.gov



NCI Antibody Portal

343 mAbs available
(2,171 units distributed)

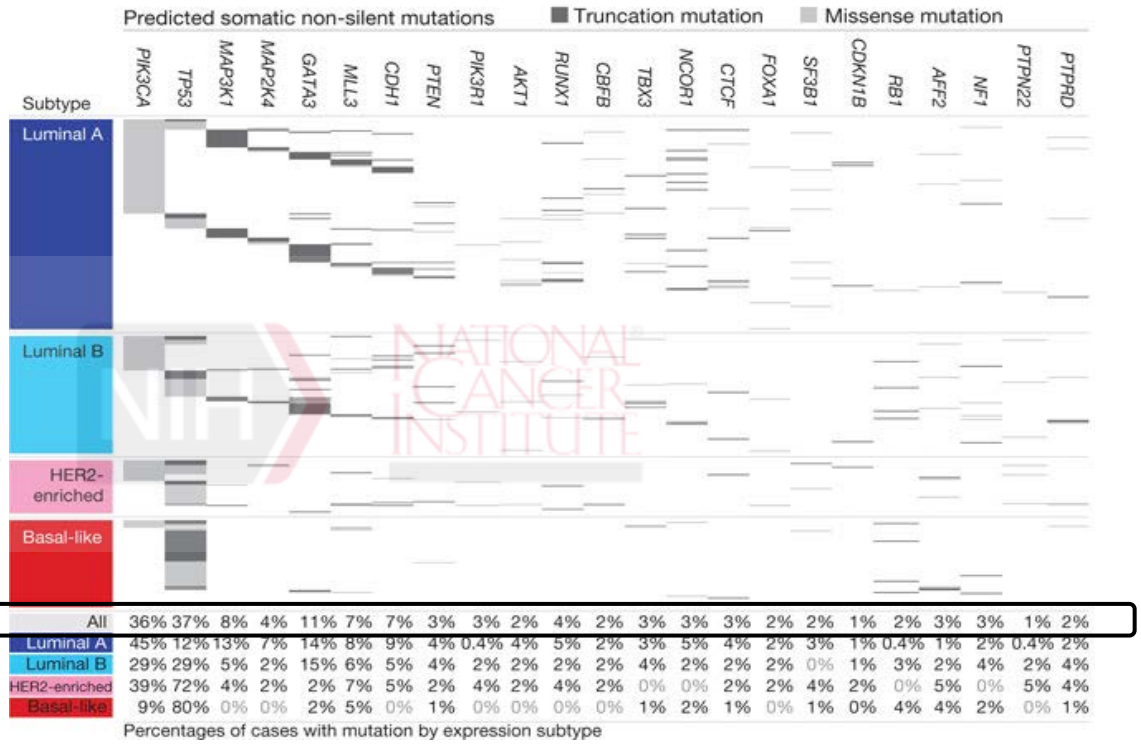
antibodies.cancer.gov



Cancer genomics aims to advance precision medicine through finding/targeting genetic alterations

- TCGA has analyzed samples from ~11,000 individuals (33 tumor types)
- Identified actionable mutations, therapies

- Not all tumors with actionable mutations respond to targeted therapy
- Many responses are temporary
- Missing biology



Complementary science for precision oncology – combining proteomic, genomic & transcriptomic analysis better elucidates the underlying biology of cancer biology and at the subtype level.

What's next for CPTAC

Two overarching goals addressing specific questions of cancer

- ***Goal 1:*** **Improve our understanding of the proteogenomic complexity of tumors**
  - Q. What's the association between genome and proteome?
  - Q. How do signaling pathway components crosstalk (DNA, RNA, and protein/PTMs)?

- ***Goal 2:*** **Improve our understanding of tumor resistance to therapy, and predicting treatment response**
  - Q. Why do some individuals not respond or relapse to therapies, when genomics indicated otherwise?

Overarching Structure of CPTAC 3.0

A. Proteome Characterization Centers

additional cancer types where questions remain on their proteogenomic complexity

5-6
new treatment-naïve cancer types

B. Proteogenomic Translational Research Centers

research models and clinical trial samples

C. Proteogenomic Data Analysis Centers

develop innovative tools that process and integrate data across the entire proteome

Data, assays and resources - community resources

Overarching Structure of CPTAC 3.0

A. Proteome Characterization Centers
additional cancer types where questions remain on their proteogenomic complexity

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B. Proteogenomic Translational Research Centers
research models and clinical trial samples

RFA-CA-15-022

C. Proteogenomic Data Analysis Centers
develop innovative tools that process and integrate data across the entire proteome

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Data, assays and resources - community resources

Governance
(Clinical Proteomic Tumor Analysis Consortium)

- CPTAC program governed by a Steering Committee (SC)
- SC serves as the primary governing body of the CPTAC program, and oversees and coordinates the activities of all PCCs, PTRCs, and PGDACs.
- The Committee will be jointly established by one representative (PDs/PIs) from each awarded PCC, PGDAC, PTRC and the NCI Program Staff.
- **Details on the composition and functions of SC are provided in each of the RFAs.**

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RFA-CA-15-021: Proteome Characterization Centers (U24)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Purpose of RFA-CA-15-021

[Section I]

- Proteome Characterization Centers (PCCs) - interactive group which use *various standardized proteomic analysis technologies* for *comprehensive* proteome-wide characterization of genomically-characterized samples provided by NCI.
- PCCs will interact with two CPTAC sub-programs: Proteogenomic Data Analysis Centers (PGDACs) and Proteogenomic Translational Research Centers (PTRCs).

URL: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-15-021.html

PCC Research Objectives

Primary Research Objective: Utilize one or more proteomic technologies to comprehensively characterize NCI-provided specimens (Discovery) and substantiate the selected targets in subsequent studies (Confirmatory).

Secondary Research Objective: Improve performance of the proteomic characterization technolog(ies)/platform(s) used in Primary Research Objective. Applicants must propose specific efforts to improve the selected technolog(ies)/platform(s) used in the PCC (pilot studies*).

*Pilot Studies: Describe overall plans; No specific pilot studies to be proposed.

NCI-supplied Biospecimens

Potential Cancer Types (goal: 5 to 6, collecting 10)

- lung adenocarcinoma
- lung squamous cell carcinoma
- pancreatic ductal adenocarcinoma
- clear cell kidney carcinoma
- cutaneous melanoma
- head and neck squamous cell carcinoma
- uterine corpus endometrial carcinoma
- sarcoma
- acute Myeloid Leukemia
- glioblastoma multiforme

Minimal amount available for each sample type:

- tumor tissue: ~25 mg wet weight per sample (and adjacent normal if available)

Patient-Derived Models Repository program (coordination with DCTD)

Human Cancer Models Initiative (coordination with CCG, DCTD, and DCB)

NCI-supported Resources

Tissue Source Sites (TSS)

Biospecimen Core Resource (BCR)

- serves as a centralized laboratory(s)
- ensure that all regulations are followed

Genomic Characterization Center (GCC)

Clinical Data Resource (CDR)

- receive, qualify, store, and distribute clinical data

Quality Management System (QMS)

- define quality processes and metrics and to track nonconforming events

Data Coordinating Center (DCC)

- central hub for all CPTAC data

Two Research Arms

Discovery:
Unbiased characterization of all detectable protein forms in discovery sample sets

Confirmation:
Quantitative proteomic assay development and measurement of selected targets identified through *Discovery* in confirmatory sample sets

Main Requirements: Both types of studies should be conducted in a high-throughput, analytically reproducible manner and be deployable at the start of the project.

Data Analysis Definitions

Level 1 (required under this FOA):

- *Discovery Proteomics Research* - Analysis of raw experimental data to generate results on peptide/protein identification and quantitation, post-translational modifications (PTMs) identification, site localization and quantitation using a reference genome;
- *Targeted Proteomics Research* - Analysis of raw experimental data to generate quantitative results on peptide/protein concentrations of the selected targets from *Discovery Proteomics Research*.

Level 2: Integration of genome-proteome data at the linear sequence level (DNA, RNA, peptides/proteins with relative quantitation obtained from Discovery Proteomics Research using personalized genomic data)

Level 3: Integration, visualization and analysis of omics data mapped onto networks and pathways obtained from Discovery Proteomics Research

Discovery Research Arm

[Section IV. Sub-section B]

Technology/platform

- Successfully been deployed and validated in at least one other site;
- Capable of generating reproducible results across laboratories in a high-throughput, large-scale study setting

Quality Assurance/Quality Control

- Detailed plan of metrics used to ensure measurement quality

Throughput

- 225 specimens per year per Center

Data Analysis

- Level 1: >6000 unique proteins per tumor sample (error rate of protein ID in the range of <10-15%)

Confirmatory Research Arm

[Section IV. Sub-section C]

Technology/platform

- Successfully been deployed in at least one other laboratory
- Capable of sampling the depth of proteomes studied that spans a wide dynamic range
- Demonstrate the analytical rigor of quantitative data obtained from within and across laboratories using standards and metrics
- It is expected that a minimum of a Tier 2 analytical characterization for mass spectrometry or an equivalent of other technologies (Reference: PMID: 24443746)

Confirmatory Research Arm
(continued)

[Section IV. Sub-section C]

Quality Assurance/Quality Control

- Detailed plan of metrics used to ensure measurement quality

Process for assay development

- Throughput (a minimum of 120 samples anticipated per year per Center)
- Quality control
- Reagents needed
- Timeline
- Expertise (personnel) involved in the process

Data analysis

- Level 1

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RFA-CA-15-023: Proteogenomic Data Analysis Centers (U24)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Purpose of RFA-CA-15-023

[Section I]

- Proteogenomic Data Analysis Centers (PGDACs) - multidisciplinary group which will provide data analysis and biological and clinical interpretation of CPTAC data.
- Awardees will be expected to develop computational tools for data analysis, data integration, and visualization and apply these tools to CPTAC data.
- PCCs will interact with two CPTAC sub-programs: Proteome Characterization Centers (PCCs) and Proteogenomic Translational Research Centers (PTRCs).

URL: http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-15-023.html

PGDAC Research Objectives

- Develop one or more computational tools to elucidate some aspects of the molecular complexity of cancer
- Apply computational tools to CPTAC data
- Identify candidates for targeted protein assays

Computational tools

- Data analysis
- Data integration
- Data visualization

What data?

Data from RFA-CA-15-021 (PCCs)

- NCI collected tumors (potential cancer types discussed in RFA-CA-15-021)
  - Genomic, proteomic, clinical data, medical imaging
- Characterization data from Human Cancer Model Initiative
- Characterization data from Patient-Derived Xenograft Repository program

Data from RFA-CA-15-022 (PTRCs)

Data Coordinating Center *and* Common Data Analysis Pipeline

Data Coordinating Center (DCC)

- Central hub for all CPTAC data
- Curates CPTAC data and metadata
- Facilitates data transfer
- Oversees common data analysis pipeline (CDAP)

Common Data Analysis Pipeline (CDAP)

- Quality control metrics for proteomic and genomic data
- Peptide and protein identification
- Peptide and protein quantification
- Common for all CPTAC data

Quality Management System

Quality Management System (QMS)

- Aids quality assurance across all CPTAC components
- Helps to define quality processes
- Tracks quality indicators
- Tracks non-conforming events

FAQs

FAQs specific to RFA-CA-15-021

FAQs specific to RFA-CA-15-021

Would applicants who may have access to biospecimens, be allowed to use these samples (in addition to NCI-supplied samples), in the generation of data under this RFA?

Answer: NCI has limited this funding mechanism to NCI-supplied samples. As outlined in the review criteria of the RFA, applications will not be evaluated based on the inclusion and/or sharing of additional applicant-provided samples.

FAQs specific to RFA-CA-15-021

Could a PCC application be a stand-alone application, or does it required that the PCC application pre-coordinate with specific PGDAC or PTRC applicants? Additionally could/should the PCC be multi-university (two or more; i.e. gathering of MS proteomics data across MS cores from different institutions)?

Answer: PCC applications are independent of PGDAC and PTRC applications. However, PCC applications should adhere and acknowledge data sharing plan and resource sharing plan required by this FOA. PCC applications can be single or multi-institutional applications as long as it meets the objectives and goals of the program.

FAQs specific to RFA-CA-15-023

FAQs specific to RFA-CA-15-023

Is it only CPTAC generated data that PGDACs should consider? What about other TCGA datasets or local data?

Answer: PGDACs may integrate other datasets with CPTAC data but other datasets should not be analyzed to the exclusion of CPTAC data.

How closely should applicants connect to "existing" PCCs?

Answer: All PCCs must recompete to become a PCC for CPTAC 3. There is no guarantee that any current CPTAC PCC will again become a CPTAC PCC in the reissuance.

FAQs specific to RFA-CA-15-023

Should proposals be limited to data that is currently supported by CPTAC and TCGA? Specifically - what might the role of image data be?

Answer: A de-identified pathology report and pathology analysis of frozen sections will be available for each CPTAC sample. Integrating proteomic data with these and other imaging modalities shall be considered responsive to the RFA.

Is it only CPTAC generated data that PGDACs should consider? What about other TCGA datasets or local data?

Answer: PGDACs may integrate other datasets with CPTAC data but other datasets should not be analyzed to the exclusion of CPTAC data.